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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,401	09/12/2005	Clifford Charles Shone	MSQ01-003-US	2849

43320 7590 03/19/2009

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EXAMINER	
GANGLE, BRIAN J	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
03/19/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,401	SHONE ET AL.	
	Examiner	Art Unit	
	Brian J. Gangle	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51-72* is/are pending in the application.

4a) Of the above claim(s) *51,54,56,59 and 72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52-53, 55, 57-58, and 60-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and remarks filed on 12/3/2008 are acknowledged. Claims 52, 55, 59-61, and 66-72 are amended. Claims 51-72 are pending. Claims 60-64, 66, and 68-71 have been amended so they now belong in Group II as set forth in the restriction requirement. Claims 51, 54, 56, 59, and 72 are withdrawn as being drawn to non-elected inventions. Claims 52-53, 55, 57-58, and 60-71 are currently under examination.

Claim Objections Withdrawn

The objection to claims 52-53, 55, 57-58, 65, and 67 because the claims are dependent on a non-elected claim, is withdrawn in light of applicant's amendment thereto.

The objection to claim 55 because the claim makes reference to *C. botulinum*, which should be italicized, is withdrawn in light of applicant's amendment thereto.

Claim Rejections Withdrawn

The rejection of claim 67 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the term "collagen-like spacer," is withdrawn in light of applicant's amendment thereto.

The rejection of claims 52-53, 55, 57-58, 65, and 67 under 35 U.S.C. 102(b) as being anticipated by Shone *et al.* (PCT Publication WO 00/28041, 2000, IDS filed 1/18/2005), is withdrawn in light of applicant's amendment thereto.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 62-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 62 is rendered vague and indefinite by the use of the terms "C3Stau2," "C3Stau1," and "C3bot." These terms are merely designations that do not reflect any specific structure. The specification refers to multiple sequences as C3Stau2; therefore, it is not clear that the descriptions of sequences found on pages 21-23 are actually definitions of these designations.

Claim 63 is rendered vague and indefinite because the claim requires SEQ ID NO:1-10 to be C3 enzymes. However, the specification describes sequences 7-10 as "C3-like" proteins. Therefore, they are not C3 enzymes.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 52-53, 55, 57-58, 60-61, and 64-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shone *et al.* (PCT Publication WO 00/28041, 2000, IDS filed 1/18/2005) in view of Lehmann *et al.* (J. Neuroscience, 19:7537-7547, 1999).

The instant claims are drawn to compositions for delivery of a therapeutic agent to a neuronal cell, comprising a therapeutic agent which inhibits at least one member of the Rho group of GTPases; a neuronal cell targeting component which comprises a Hc domain of botulinum C1 toxin or a fragment thereof which retains the function of the native Hc domain, wherein the Hc domain has been made recombinantly; and a domain for translocation of the therapeutic agent into a cell, wherein the translocation domain comprises botulinum C1 toxin and fragments thereof, and wherein the therapeutic agent is an ADP-ribosyltransferase.

Shone *et al.* disclose a composition for delivery of a therapeutic agent (superoxide dismutase), linked to a neuronal cell targeting component that comprises a first domain that binds to a neuronal cell and a second domain that translocates the therapeutic agent into the neuronal cell (see abstract). Shone *et al.* disclose that their construct is made recombinantly (page 6, line 26) and describes the binding domain and the translocation domain as coming from

a clostridial neurotoxin, including serotype C1 (page 12, line 23 through page 14, line 15). Shone *et al.* also disclose the use of a linker molecule between the therapeutic agent and the toxin, where the linker is a peptide with the sequence CGLVPAGSP, which corresponds to SEQ ID NO:23 of the instant application (page 10, lines 20-23). Shone *et al.* also disclose the construct as both a single chain polypeptide and a di-chain polypeptide (page 16, lines 20-25). Shone *et al.* state that the construct allows the therapeutic molecule to be transported into neuronal cells (page 7, lines22-25) after specific binding to neuronal tissue (page 12, lines 1-5). The construct can be produced in a pharmaceutically acceptable liquid or as a suspension, emulsion, solution, or freeze-dried powder (page 12, lines 15-21).

Shone *et al.* differs from the instant invention in that the therapeutic agent is disclosed as superoxide dismutase, rather than an ADP-ribosyltransferase.

Lehmann *et al.* disclose C3 enzymes from *Clostridium botulinum* that are ADP-ribosyltransferases (page 7538, first paragraph). Lehmann *et al.* show that delivery of these enzymes to neuronal cells causes regeneration of axons (see abstract and page 7538, first paragraph). Lehmann *et al.* also state that growing or mature axons may not take up C3 efficiently and that antagonists of RHO activity that can cross the plasma membrane of these cells may improve the extent of regeneration (page 7546, final paragraph).

It would have been obvious to one of ordinary skill in the art, at the time of invention, to use the C3 enzyme disclosed by Lehmann *et al*. in the targeting and translocation construct of Shone *et al.* because Lehmann *et al*. disclose that C3 causes regeneration of axons and such a construct would improve the extent of regeneration.

One would have had a reasonable expectation of success because Lehmann *et al.* showed that delivery of C3 to neuronal cells led to axonal regeneration and because Shone *et al.* showed that the construct was capable of delivering an agent into neuronal cells.

Claims 52-53, 55, 57-58, 60-61, and 63-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shone *et al.* (PCT Publication WO 00/28041, 2000, IDS filed 1/18/2005) in view of McKerracher (US Patent 6,855,688, 2005, filed on 4/9/2002).

The instant claims are drawn to compositions for delivery of a therapeutic agent to a neuronal cell, comprising a therapeutic agent which inhibits at least one member of the Rho

group of GTPases; a neuronal cell targeting component which comprises a Hc domain of botulinum C1 toxin or a fragment thereof which retains the function of the native Hc domain, wherein the Hc domain has been made recombinantly; and a domain for translocation of the therapeutic agent into a cell, wherein the translocation domain comprises botulinum C1 toxin and fragments thereof, and wherein the therapeutic agent is an ADP-ribosyltransferase.

Shone *et al.* disclose a composition for delivery of a therapeutic agent (superoxide dismutase), linked to a neuronal cell targeting component that comprises a first domain that binds to a neuronal cell and a second domain that translocates the therapeutic agent into the neuronal cell (see abstract). Shone *et al.* disclose that their construct is made recombinantly (page 6, line 26) and describes the binding domain and the translocation domain as coming from a clostridial neurotoxin, including serotype C1 (page 12, line 23 through page 14, line 15). Shone *et al.* also disclose the use of a linker molecule between the therapeutic agent and the toxin, where the linker is a peptide with the sequence CGLVPAGSP, which corresponds to SEQ ID NO:23 of the instant application (page 10, lines 20-23). Shone *et al.* also disclose the construct as both a single chain polypeptide and a di-chain polypeptide (page 16, lines 20-25). Shone *et al.* state that the construct allows the therapeutic molecule to be transported into neuronal cells (page 7, lines22-25) after specific binding to neuronal tissue (page 12, lines 1-5). The construct can be produced in a pharmaceutically acceptable liquid or as a suspension, emulsion, solution, or freeze-dried powder (page 12, lines 15-21).

Shone *et al.* differs from the instant invention in that the therapeutic agent is disclosed as superoxide dismutase, rather than an ADP-ribosyltransferase.

McKerracher discloses C3 enzymes from *Clostridium botulinum*, which, when delivered intracellularly, can stimulate regeneration of injured axons (see column 1, lines 20-30 and column 2, lines 25-40). McKerracher discloses that C3 does not easily penetrate the plasma membrane of living cells (column 3, lines 48-52). C3 enzymes disclosed by McKerracher include the protein encoded by SEQ ID NO:36 and 42, which match the instantly claimed SEQ ID NO:6 at residues 46-228.

It would have been obvious to one of ordinary skill in the art, at the time of invention, to use the C3 enzyme disclosed by McKerracher in the targeting and translocation construct of

Shone *et al.* because McKerracher discloses that C3 causes regeneration of axons when delivered intracellularly.

One would have had a reasonable expectation of success because McKerracher showed that delivery of C3 to neuronal cells led to axonal regeneration and because Shone *et al.* showed that the construct was capable of delivering an agent into neuronal cells.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571)272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Brian J Gangle/
Examiner, Art Unit 1645

/Mark Navarro/
Primary Examiner, Art Unit 1645